PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	See form PCT/ISA/210
Applicant's or agent's file reference 4060 PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/001037	02.02.2005	03.02.2004

International Patent Classification (IPC) or both national classification and IPC
G01N33/68, G01N33/569, C12Q1/28

Applicant
B.R.A.H.M.S AKTIENGESELLSCHAFT

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/001037

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/001037

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	2	YES
	Claims	1, 3-12	NO
Inventive step (IS)	Claims		YES
	Claims	1-12	NO
Industrial applicability (IA)	Claims	1-12	YES
	Claims		NO

2. Citations and explanations:

The following documents (D) cited in the search report are mentioned in this opinion; the same numbering will be used throughout the procedure:

D1: EP-A-0 217 542 (UBE INDUSTRIES) 8 April 1987 (1987-04-08)

D2: GALIKOWSKI M ET AL: "A comparative study of cholecystectomy, antibiotic prophylaxis and sepsis in polymorphonuclear free radical generation and superoxide dismutase activity in rabbits" RESEARCH IN SURGERY 1994 SPAIN, Vol. 6, No. 1, 1994, pages 31-34, XP008031741 ISSN: 0214-5987

D3: WO 94/22016 A (REPINE JOHN E; LEFF JONATHAN A (US)) 29 September 1994 (1994-09-29)

D4: WARNER ANN ET AL: "Prognostic role of antioxidant enzymes in sepsis: Preliminary assessment" CLINICAL CHEMISTRY, Vol. 41, No. 6 PART 1, 1995, pages 867-871, XP001189668 ISSN: 0009-9147

1 Novelty

1.1 D1 discloses (the references between parentheses refer to this document):
A method for early determination of the mortality risk of patients (stomach cancer patients, see abstract), characterized in that the concentration of Cu/Zn superoxide dismutase in a serum or plasma sample of a patient is determined selectively and, when above a preset threshold, is correlated with a high mortality risk (cancer risk) (claim 3, figure 5).

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The subject matter of claim 1 is therefore not novel in the light of D1. Dependent claims 3-12 likewise appear not to be novel or inventive in the light of D1.

1.2 Claim 2 is to be regarded as novel in the light of the cited prior art because none of the cited documents discloses the determination of the concentration of SOD-1 in sepsis patients.

2 Inventive step

2.1 Document D2 is regarded as the closest prior art to the subject matter of claim 2. It discloses (the references between parentheses refer to this document):
A method for early determination of the mortality risk of sepsis patients (page 31, column 1, line 7 to the end of the page, page 34, column 1, lines 10 to 17), characterized in that the activity of Cu/Zn superoxide dismutase [SOD-1] is determined in a serum or plasma sample of a patient (page 32, column 2, paragraph 3) and, when above a preset threshold (tables 1 and 2), correlates with a high mortality risk (page 34, column 1, lines 10 to 17).
The difference between the present application (claim 2) and D2 is the determination of the SOD-1 **concentration** in human patients. The difference has the effect that factors which might influence the SOD-1 activity are inoperative. The objective problem can therefore be stated to be: how can a method be provided for detecting sepsis in humans with elimination of factors interfering with the enzymic activity?
The solution is not regarded as inventive for the following reasons:
D1 (see claim 1) has disclosed antibodies against human SOD-1 to a person skilled in the art. It is moreover generally known that measurement of enzymic activities may be of unreliable accuracy owing to interfering factors which may be present in biological samples such as serum and plasma. It would therefore be obvious to a person skilled in the art to combine the teachings of documents D2 and D3 and achieve the aim.

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

In addition, D3 discloses that superoxide dismutases (SOD-2, see abstract) can efficiently be determined using antibodies.

2.2 D4 can also be taken as the closest prior art:
It discloses (the references between parentheses refer to this document):
A method for early determination of the mortality risk of sepsis patients (abstract), characterized in that the activity of superoxide dismutase (SOD-1, -2 and -3, see page 868, column 2, lines 4 and 5) is determined in a serum or plasma sample of a human patient and, when above a preset threshold, correlates with a high mortality risk.
The difference between the present application (claim 2) and D4 is the determination of the concentration of only one of the dismutases (SOD-1). The effect of this difference is to eliminate factors interfering with the enzymic activity. The objective problem can therefore be stated to be: how can a method be provided for detecting sepsis with elimination of factors interfering with the enzymic activity? The solution, the detection of the SOD-1 concentration, is not inventive for the following reasons:
A person skilled in the art knows from D3 that, instead of determining the enzymic activity of superoxide dismutases 1-3, sepsis can be detected by determining the concentration of only one dismutase (SOD-2, see D3). It would therefore be obvious to a person skilled in the art also to assay SOD-1 (or SOD-3). The solution provided by the present application is thus not inventive in the light of D4 and D3 either.

2.3 The subject matter of claims 1-12 is to be regarded as industrially applicable.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2005/001037

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

1 Claim 1 is not, as required by PCT Article 6, supported by the description because its scope goes beyond the scope justified by the description and the drawings. The reasons for this are as follows: the experimental results on which the application is based relate merely to sepsis patients. However, limitation of the claims to sepsis takes place not in independent claim 1 but only in dependent claim 2. This also makes claim 8 unclear when it speaks of a **further sepsis** prognosis parameter.

1.1 The feature "patients in **intensive care units or emergency departments**" is unclear because it would be difficult for a person skilled in the art to decide whether a patient is covered by this definition. The scope of protection of claim 1 is therefore likewise unclear.